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09/892,591	06/27/2001	Tillman U. Gerngross	GFI 100	2292

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/892,591	GERNGROSS, TILLMAN U.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2004*.

2a)☒ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,39,40,42-50,52-54 and 57-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,39,40,42-50,52-54 and 57-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6/27/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 35, 39, 40, 42-50, 52-54 and 57-73 are pending in the application.

This Office Action is in response to the Amendment filed on 7/12/04.

Response to Amendment

The objection to the specification has been withdrawn in light of Applicant's amendment.

The rejection of claims 35-57, 59, 60, 62-64 under 35 U.S.C.112 2nd paragraph has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 35-42, 46-48, 52, 54-56, 59 and 60 under 35 U.S.C.102 (b) has been withdrawn in light of Applicant's amendment of the claims.

Claims 35, 39, 40, 42-50, 52-54, 57-64 and newly added claims 65-73 stand rejected under 35 U.S.C. 112 1st paragraph for reasons set forth of the record mailed on 3/12/04 and further discussed below.

The rejection of claims 58 and 61 under 35 U.S.C.112 2nd paragraph is maintained for reasons set forth of the record mailed on 3/12/04 and further discussed below.

Claims 35, 39, 40, 42-50, 52-54, 57-70 are rejected under 35 U.S.C. 112, second paragraph for reasons set forth below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 39, 40, 42-50, 52-54, 57-64 and newly added claims 65-69, 71-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly added claims 65-69 are rejected for same reasons as set forth of the record mailed on 3/12/04 and further discussed below.

In response to this rejection, Applicants argue that a persons skilled in the art would comprehend and be able to make or identify a variety of other lower eukaryotic host cells lacking 1, 6 mannosyltransferase activity using techniques well known in the art and the teaching of the specification. Applicants further argue that the term "lower eukaryotic cell" provides the "structural" characteristics, whereas the term "that does not display alpha-1, 6 mannosyltransferase activity with respect to the N-glycan of a glycoprotein" functionally modifies that art-defined structure, and such disclosure is sufficient for the written description requirement. Moreover, Applicants argue that mutagenesis and classical screen method can be used to produce lower eukaryotic host cell that lack alpha-1,6 mannosyltransferase activity. Lastly, Applicants cited Maras et al. to demonstrate that other lower eukaryotic host cells lacking alpha-1, 6 mannosyltransferase activity (*Trichoderma* and *Aspergillus*) were known at the time of filing. Applicants further present data which show other species of "lower eukaryotic host cell" such as *Kluyveromyces lactis* and *Aspergillus niger* lacking alpha-1, 6 mannosyltransferase. Therefore, Applicants conclude that the written description requirement is met.

These arguments have been fully considered and deemed partially persuasive. The specification defines the term "lower eukaryotes" as a unicellular or filamentous fungus. Since the specification and the exhibits submitted by Applicants teach 5 species of this claimed genus (either with natural mutation or genetic manipulation) to demonstrate the structural functional relationship between the lower eukaryotic host cell and the functional property of lacking of alpha 1, 6 mannosyltransferase expression which results in lack of production of long mannose chain glycoprotein, the written description requirement is considered met for this term. However, the claim recite "a lower eukaryotic host cell that does not display a 1, 6 mannosyltransferase activity with respect to the N-glycan on a glycoprotein." The specification does not disclose a lower eukaryotic host cell lacking any activity of other 1, 6 mannosyltransferase with respect to N-glycan of the glycoprotein. The art does not teach such claimed genus of host cells. As such, the specification does not provide sufficient written description for this term. Newly added claims 65-69, 71-73 also recite this term. Therefore, they are rejected for same reasons as discussed in previous office action and above.

In response to the rejection with regard to the term "one or more enzymes of the production of a Man5GlcNAc2 carbohydrate structure," Applicants amended the claims to recite "a mannosidase enzyme for the production of a Man5GlcNAc2 carbohydrate structure." Applicants further argue that only an alpha 1, 2 mannosidase enzyme will catalyze the conversion of Man8GlcNAc2 to Man5 GlcNAc2, and alpha 1, 2 mannosidase from other species of unicellular or filamentous fungus are taught in the specification. Therefore, Applicants conclude that the written description requirement is met.

These arguments have been fully considered but deemed unpersuasive. Upon careful review of the pending claims (include newly added claims 65-69), none of the claim recites "a mannosidase enzyme for the production of a Man5GlcNAc2 carbohydrate structure." Further, the claims do not recite or specify that the Man5GlcNAc2 is converted from the Man 8GlcNAc2 structure as a substrate. Although the specification provides a number of alpha 1, 2 mannosidase from different species, it still does not satisfy the written description requirement for any hybrid mannosidase enzymes as claimed for same reasons discussed in the previous office action. As such, the rejection is maintained for the hybrid mannosidase.

Claims 35, 39, 40, 42-50, 52-54, 57-64 and newly added claims 65-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing humanized glycoprotein in a lower eukaryotic host cell that does not have 1,6 mannosyltransferase, the method comprising introducing a vector encoding a protein of interest into the host cell, co-transfecting a construct encoding an alpha-1,2 mannosidase selected to have a pH optimum within 1.4 pH units of the average pH optimum of glycosylation-related enzyme in the subcellular location operably linked to a targeting signal to said subcellular location, wherein the protein of interest comprises more than 30% of Man5GlcNAc2 structure is produced; co-transfecting a construct encoding GnT1 selected to have a pH optimum within 1.4 pH units of the average pH optimum of glycosylation-related enzyme in the subcellular location operably linked to a targeting signal to said subcellular location, wherein the protein of interest has a humanized glycoform GlcNAc-(Man)5-(GlcNAc)2. And a for a method for producing humanized glycoprotein in a lower eukaryotic host cell that does not have 1,6 mannosyltransferase, the method comprising introducing a vector encoding a protein of interest

into the host cell, co-transfecting a construct encoding an alpha-1,2 mannosidase I and II selected to have a pH optimum within 1.4 pH units of the average pH optimum of glycosylation-related enzyme in the subcellular location operably linked to a targeting signal to said subcellular location, wherein the protein of interest comprises more than 30% of Man5GlcNAc2 structure is produced; co-transfecting a construct encoding a N-acetylglucosaminyl transferase I and II, an UDP-Acetylglucosamine transporter selected to have a pH optimum within 1.4 pH units of the average pH optimum of glycosylation-related enzyme in the subcellular location(s) operably linked to a targeting signal to said subcellular location, wherein the protein of interest has a humanized glycoform GlcNAc2Man3GlcNAc2; does not reasonably provide enablement for a method for producing any type of humanized protein with any type of complex glycoprotein structure (even when the intermediate Man5GlcNAc2 structure is produced). The specification also fails to enablement a method of producing a humanized protein in a lower eukaryotic host cell without introducing exogenous construct encoding such protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The newly added claims 65-73 are rejected for same reasons as set forth of the record mailed on 3/12/04 and further discussed below. Claims 71-73 are further rejected because the specification does not teach how to convert long mannose chain N-glycan structure to humanized glycoprotein without the trimming by mannosidase first to produce the intermediate Man5GlcNAc2 structure. According to the teaching of the specification, introducing a hybrid N-acetylglucosaminyltransferase alone will not result in a humanized glycoprotein since the yeast glycoprotein is not a substrate for this enzyme.

In response to the enablement rejection, Applicants argue that the invention solves the problem of inefficiency in the prior art methods. Applicants assert the instant invention involves introducing into host cell a hybrid glycosylation enzyme that has been selected for the ability of the catalytic domain and targeting sequence to work together optimally at the location in the host cell. Applicants further assert that the instant invention not only increases production of Man5GlcNAc2 structure, but also allowed for the further modification to GlcNAcMan5GlcNAc2 *in vivo*. Furthermore, Applicants assert that other hybrid enzyme of glycosylation can also be introduced in the same way as the mannosidase as taught by the instant specification. Moreover, Applicants submit post filing date evidence to support the enablement of the claimed methods. Applicants assert that subsequent work by Applicant demonstrate that 40%-60% of Man5GlcNAc2 are produced by following the method taught by the instant specification, using hybrid sequence of human mannosidase B fused to targeting sequence of S. cerevisiae, whereas 60%-80% of the Man5GlcNAc2 are produced using hybrid sequence of mouse mannosidase fused to an Och1p targeting sequence. Applicants further cite Choi et al. for production of glycans from strains engineered with targeted mannosidase and demonstrate the production of Man5GlcAc2 in excess of 30%. Lastly, Applicants cite Hamilton et al. to demonstrate that high efficiency production of Man5GlcNAc2 structure and subsequent conversion of such structure to GlcNAc2Man3GlcNAc2, a human like glycoprotein structure. Applicants thus conclude that the invention is enabled by the instant specification.

These arguments have been fully considered and deemed partially persuasive. As discussed in the previous office action, the specification itself does not provide sufficient enablement for the claimed invention. However, considering the results obtained from the post

filing date references, the claimed invention is considered enabled to the extend as indicated above. On the other hand, the protocols employed by the Choi et al. and Hamilton et al. do not reflect the broad scope of the claimed method. As such, they cannot support the enablement of the method to their full scope. Both references teach utilization of a construct encoding a reporter protein, K3, that is introduced into the yeast for measurement of the production of human-like protein. Whereas the claimed method does not tell where this human like protein comes from. The claimed method is not enabled for producing all the yeast endogenous protein in human like glycoprotein form. Choi et al. further teaches introducing vectors encoding specific enzyme GnT1 localized to specific location in P.pastoris, Golgi, that is responsible for the production of human like glycoprotein, GlcNAc-(Man)5-(GlcNAc)2 structure. Similarly, Hamilton et al. teach a number of enzymes mannosidase I, II, N-acetylglucosaminyl transferase I and II, UDP-N-acetylglucosamine transporter targeted to specific location in the P.pastoris, such as ER, Golgi, and subsequent production of GlcNAc2Man3GlcNAc2, a human like glycoprotein structure. In view of the complex nature of producing human like glycoprotein, successful production of human like protein in lower eukaryotes is unpredictable (see detailed reasons in previous office action). Although the specification states that the claimed method is an improvement over prior art, it still has to set forth specific working examples to demonstrate the enablement of the claimed invention. As such, the claimed method is enabled to the extend of what is demonstrated in the Choi et al. and Hamilton et al.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 58 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response to this rejection, Applicants assert that the term "derived" is deleted from the claims.

Upon review of the pending claims 58 and 61, the term "derived" is still recited in the claims. Therefore, this rejection is maintained for same reason as discussed in the previous office action.

New Grounds of Rejection Necessitated by the Amendment

Claim Rejections - 35 USC § 112

Claims 35, 39, 40, 42-50, 52-54, 57-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 35, 39, 40, 42-50, 52-54, 57-70 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps involved in the conversion of intermediate structure Man5GlcNAc2 to a humanized form of glycoprotein. The method is incomplete because the Man5GlcNAc2 is only an intermediate, not a final humanized glycoprotein product.

Regarding claims 42 and 43, the recitation of "fewer than four/six mannose residue" renders the claim indefinite because the definition of a humanized protein is unclear. The

specification defines a humanized glycoprotein as a protein has N-glycan structure with fewer than four mannose residue. It appears to be redundant to recite a new limitation of fewer than four mannose residue if the humanized glycoprotein already has a N-glycan less than four mannose. It is even more confusing how this humanized glycoprotein can have more than four mannose as implied by the recitation of "fewer than six mannose residue." As such, the metes and bounds of the claim is not clear.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER